Manual of Operations

MOOP

Data Collection on Adverse Events of Anti-HIV Drugs

Version of MOOP: Version 1.4 2013*
(* Differs from Version 1.3 with change of address and personnel at the coordinating centre in Copenhagen, addition to the definition of diabetes mellitus, addition of the 3 new endpoints, change in name of chronic liver disease (CLD) to end-stage liver disease (ESLD), chance in name from non-AIDS defining cancer (NADM) to cancer (both AIDS- and Non-AIDS defining cancers), removal of guidelines for the completion of a general D:A:D event form, addition to the monitoring requirements and specification of the requested source documentation for events. Also updated are all case report forms in relation to the logistic information and for:
MI: question added regarding any ICP event(s) in relation to the MI
Stroke: question regarding stroke duration specified into binary variable
DM: addition to the DM definition
ESLD: change in event name and specification of case requirements
ESRD: addition of requested source documentation
Cancer: change in event name
CoDe: addition of requirements of completing designated D:A:D event forms in addition to the CoDe form)

Updated: January 2013

Participating cohort studies:
EuroSIDA, (32 European countries plus Israel and Argentina); SHCS, (Switzerland);
ICONA, (Italy); ATHENA Cohort, (The Netherlands);
CPCRA, (USA); Nice Cohort, (France); Aquitaine Cohort, (France);
HivBivus, (Sweden); BASS Cohort, (Spain);
AHOD, (Australia); Brussels St. Pierre Cohort (Belgium)

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The following Sections have been revised:

Section 1: Update of study presentation

Section 1.2: Update on contact information for staff at the coordinating centre

Section 3.2: Former section regarding completion of the general (precursor) D:A:D Event Form removed

Section 3.3.-3.8 Guidelines for the completion of events forms and all individual event forms (including the CoDe form) updated

Section 3.7 and 4.6: Update on the definition of diabetes mellitus

Section 3.3 and 4: The 3 new endpoints described in "Guidelines for completion of the 3 new endpoints in the D:A:D study Cancers, End-stage Liver Disease, End-stage Renal Disease version 1.0:18 February 2009" have been included in the MOOP section 4.

Section 7: Update of Monitoring with specification of alternatives to 10% random monitoring

Appendix A: Addition of new anti-diabetic agents

Appendix F: New appendix with guide to requested source documentation

Appendix G: New appendix with references

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1 Presentation/Introduction

The cohort study: **D**ata Collection on **A**dverse events of Anti-HIV **D**rugs (D:A:D) is a prospective multi-cohort study of HIV-1 positive individuals under active follow up. 11 cohorts across the world are participating and the study has enrolled more than 49.000 patients in 3 enrolment cohorts.

The study period in D:A:D has been extended and is projected to last at least until 2017.

The purpose of the study is to evaluate the long-term side effects of antiretroviral therapy by looking at the incidence of a number of clinical endpoints among HIV-1 positive individuals. The main study objective is assessment of incidence and risk of myocardial infarction (MI) and other cardiovascular diseases (CVDs) in relation to antiretroviral treatment. In recent years focus has expanded to also include the 3 endpoints: Cancers, End-stage renal disease (ESRD) and End-stage liver disease (ESLD).

A milestone of the D:A:D study was the identification of an increased risk of myocardial infarction with increasing duration of combination antiretroviral therapy (cART).(NEJM, 2003;349(21); 1993-2003). As the D:A:D study continues to accumulate follow-up time, our ability to describe the exact nature of the relationship between cART and these co-morbidities, and to describe the extent, to which this relationship can be explained by metabolic changes, will increase.

The data collection includes information on patients´ conventional cardiovascular risk factors and previous diseases such as myocardial infarction, stroke, diabetes mellitus, hereditary tendency, smoking, fat redistribution, etc.

In each of the participating cohorts, the data collection takes place at least every 8 months. Data is computerised by each cohort and subsequently merged in a central database at the (Coordinating Centre) CC in Copenhagen.

Support for the study is given by the Oversight Committee for The Evaluation of Metabolic Complications of HAART, and several pharmaceutical companies producing antiretroviral drugs contribute financially.

The CC located at Copenhagen HIV Programme (CHIP), has the overall responsibility for the conduct of the study. However, the study is supervised by a Steering Committee (SC) represented by members of each participating cohort.

The CC has established guidelines and instructions for the conduct of the study. This quality assurance is implemented in the D:A:D protocol and operationalised in this Manual Of Operations (MOOP).

1.1 Abbreviations

ADA – American Diabetes Association
CC – Coordinating Centre
CHIP – Copenhagen HIV Programme
CK – Creatinine Kinase
CK-MB – Creatinine Kinase - Myocardial Bound
CoDe – Coding Causes of Death in HIV
CRF – case report form/event form/event checking chart
CSF – Cerebrospinal Fluid
D:A:D – Data Collection on Adverse events of Anti-HIV Drugs
ECG – Electrocardiogram
HAART – Highly Active Antiretroviral Therapy
cART – combination Antiretroviral Therapy
LDH – Lactate Dehydrogenase
MOOP – Manual of Operations
NGSP – National Glycohemoglobin Standardization Program
PTCA – Percutaneous Transluminal Coronary Angioplasty / Stent
SAH – Subarachnoid haemorrhage
SOP – Standard Operating Procedure
TIA – Transient Ischemic Attack
WBC – White Blood Cells

1.2 Contact information for the Coordinating Centre (CHIP)

Address:

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Principal Investigator: Jens Lundgren, MD, DMSc, Professor, Email: jdl@cphiv.dk

2 Data Collection

The principal investigator (PI) at each site is responsible for the data collection for the D:A:D study including completion of case report forms. However, the responsibility of completing the case report forms can be delegated to other study personnel (e.g. study nurses). When the case report forms are completed, please ensure that data are entered correctly in accordance with procedures already implemented by the cohort and of the highest possible standard.

2.1 Data Management

Data for the D:A:D study are collected at each site by study personnel completing the case report at least every 8 months in addition to the already existing data collection in the cohorts (for details see section 2.2). Subsequently, data are submitted to the respective cohort coordinating office and computerised. At this point, data are transferred electronically by each cohort to the CC in Copenhagen. A data manager affiliated with the CC is responsible for merging all data into a central database to which there is limited access in order to uphold data safety and confidentiality.
A standard operating procedure (SOP) has been developed for the management of the data, detailing the data format and the procedures for electronic transfer. This SOP is available at the Cohort Coordinating Center and at www.cphiv.dk.
Throughout the study, the quality of the data is assessed by site and cohort monitoring to ensure a valid data collection (see section 7).

2.2 Basic data collection

The data collection for the D:A:D study includes all items specified in the case report forms. In addition, it is required that all participating cohorts have the ability to provide supplementary data that includes the following:
- Gender
- Race (if available)
- Mode of infection
- Documented HIV antibody test
- Weight (at least once annually)
- Height
- Complete antiretroviral treatment (date of initiation, date of discontinuation, reason for discontinuation (a list of reasons for discontinuation can be found in section 5)
- Information on disease specific prophylaxis against *Pneumocystis carinii (jiroveci) pneumonia, Toxoplasmosis* and *Mycobacterium avium complex.*
- Opportunistic infections
- CD4 cell count/ plasma HIV viral load (>3 measurements per year)
- Blood pressure measurements
- Laboratory measurements
- Hepatitis Virology/Serology
- HIV related events (CDC group C)
- Death *(novel data-collection on specific causes of death – please refer to section 6 and to the CoDe Protocol)*

3 Guidelines for completion of forms used in D:A:D

3.0 Guidelines for completion of enrolment forms

ITEM 1: Diseases/procedures ever diagnosed/performed
Please check carefully whether the patient has ever experienced one or more of the diseases referred to in this section. If the patient has been diagnosed with the same disease at several occasions, please record the date the disease was first diagnosed. This also implies the performance of procedures. Diseases that occurred before enrolment to the D:A:D study do not have to fulfil the detailed case definitions of endpoints in the D:A:D study (however, very important during follow up) – diagnoses and procedures made previously are accepted. Please note that a stroke event in D:A:D covers cerebral infarction *and* cerebral haemorrhage. The answer no covers: the disease /procedure has never been diagnosed/performed. The information should be obtained from patient interview and/or review of the patient record. The box unknown should *only* be ticked if data are missing in the patient record or in cases of uncertainty (unable to interpret data).

ITEMS 2-8 on the enrolment form are the same as for the Follow-up form. Please see section 3.1, Guidelines for completion of follow-up forms.

3.1 Guidelines for completion of follow-up forms

The following contains information and clarification of the items in the follow-up form, and the event checking charts. Of note, most cohorts have incorporated the follow-up form in their standard data collection forms. Thus the order of the items listed below may be different depending on the cohort. The information should be obtained from patient interview and/or review of the patient record. The answer 'no' means the disease /procedure has never been diagnosed/performed. The box unknown should *only* be ticked if data are missing in the patient record or in cases of uncertainty (unable to interpret data).

ITEM 1: Diseases/procedures diagnosed/performed since last follow up
Please find case definitions in Section 4. Note that these diagnoses should only be applied when patients fulfil these criteria. In cases of doubt, please contact the Cohort Coordinating Centre. If one of the diseases has occurred or one of the surgical procedures listed has been performed since last follow up, a standardised event checking chart must be submitted to the Cohort Coordinating Centre "real time" (Section 3.2/Appendix B).

ITEM 2: Myocardial infarction or stroke experienced by first-degree relatives
The data collection only includes myocardial infarction or stroke experienced by first-degree relatives *before* the age of 50 years. Please note that a stroke event in D:A:D covers both cerebral infarction *and* cerebral haemorrhage.

ITEM 3: Blood samples
Preferably, the blood tests (serum glucose, total cholesterol, serum HDL cholesterol and serum triglycerides) are collected when the patients are fasting. If there is any doubt at the time of blood drawn, please leave the box 'fasting' empty. Additional blood tests collected are ALT, AST, total bilirubin, platelet counts, albumin, creatinine, haemoglobin

ITEM 4: Blood pressure
Please enter the last measured systolic and diastolic blood pressure. The unit for blood pressure measurement is mmHg.

ITEM 5: Ongoing treatment
Drugs within the different groups (anti-platelets, ACE inhibitors, other antihypertensive agents, lipid lowering agents, insulin or derivatives hereof, oral antidiabetic agents and anabolic steroids/appetite stimulants) are specified.
Please find medication lists in appendix A. Medications that are not listed in the MOOP will not be a part of the data collection.

ITEM 6: Cigarette smoking
For this study, the definition of a regular cigarette smoker is a person who smokes cigarettes at least every other day (more than 3 days a week).
Only cigarette smokers are of interest. If someone smokes cigars or a pipe, please answer '**no**' to this question**.**

ITEM 7+8: Fat redistribution
The assessment of development of fat redistribution is based on evidence of fat accumulation or loss of fat by physician's examination *and* patient's confirmation hereof.

Indication of dates in the follow-up forms
*If the month is unknown, please write **07** and the year in the box. If the year is unknown a code is not requested, please leave the box empty.*
For the event form: Exact date is required.

3.2 Guidelines for completion of event forms and background for the 3 endpoints included in 2008 (reporting baseline 2004)

The case report forms are of crucial importance for the reporting of the study endpoints and are further necessary for the validation process. The reporting is the responsibility of the investigator at each site, with reference to the individual Cohort Coordinating Centre.
The CC in Copenhagen should be notified about these events as soon as possible after the event has occurred ("real time") and no later than 8 weeks after occurrence

All event checking charts:
Page header: Please complete this section with centre, cohort and patient identification at the top of the page.
Page footer: Please sign and date the form before sending it to the D:A:D CC.
The CC should keep a copy of the form on file.
(Refer to instructions regarding 'Route of communication - event checking charts, section 3.11).

All D:A:D event forms are available online at:
http://www.cphiv.dk/DAD/StudyDocuments/tabid/112/Default.aspx

If you have questions to D:A:D please contact the CC at: www.cphiv.dk or call + 45 35 45 57 57

Background for the addition of Cancers, End-stage Liver Disease, and End-Stage Renal Disease in 2008:
The D:A:D study expanded the protocol in 2008 to include 3 new non-fatal endpoints: Cancers, End-stage Liver Disease, and End-Stage Renal Disease.
The rationale behind this was to better assess the possible association of cART treatment with the risk of different organ diseases and cancer, the data-collection is at this stage expanded to also include the non-fatal outcomes. The baseline for the reporting of events of these 3 endpoints is *1st January 2004.*

Cancer
More than 60 % of all deaths in HIV-1 positive individuals receiving cART is from causes other than AIDS (1-7). In the D:A:D study covering the period from 1999-2007, 12% of all deaths in persons on cART were due to cancers. Several studies have suggested observation of higher rates of a number of cancers in HIV-positive individuals as compared with the background population, in particular in immunodeficient stages (8-10).
The primary objective of the D:A:D study regarding cancers is to assess the possible relationship between exposure to cART and risk of cancers (overall and according to most prevalent types). Secondary objectives include an assessment of the possible associations between immunodeficiency and the risk of cancers.
Initially the D:A:D study collected only Non-AIDS Defining Malignancies on the designated event form. The AIDS-defining cancers were reported electronically only as part of the record for AIDS defining events. Newer studies do not fully justify a division of cancers into AIDS- and non-AIDS defining cancers, therefore beginning 1st January 2013 the case-report form "Non-AIDS Defining Malignancies" was renamed "Cancer, both AIDS and Non-AIDS defining". This event form should include all malignancies (apart from pre-cancers, relapses, squamous and basal cell skin cancers).

End-stage Liver Disease
Untreated HIV, as well as several other immunodeficiency disorders, can lead to acceleration of liver disease seen in individuals chronically infected with either hepatitis B or hepatitis C virus (11-16). The D:A:D study has previously found that longer exposure to cART is associated with a slight increase in the risk of liver mortality.
As the number of patients co-infected with hepatitis B virus and/or hepatitis C virus is large, it is important to further explore if continued exposure to cART may ultimately lead to significant progression of liver failure. With longer follow-up and the inclusion of non-fatal outcomes of liver disease, the study will in the future be able to investigate whether clinically significant treatment-associated liver disease occurs.

End-stage Renal Disease
Several ARVs used to treat HIV and its' complications are suspected to be nephrotoxic. Some of these ARVs may exert acute and completely reversible impairment of renal function, but effects of long-term exposure had not been properly explored. Recent studies suggest that exposure to some of these ARVs may lead to permanent impairment of the kidney function in some patient subgroups.

3.3 Event checking chart for cases of myocardial infarction (MI)

To be completed for patients who have experienced a myocardial infarction (MI) (definitive or possible, fatal and non-fatal cases). For fatal cases, please also complete the 'CoDe reporting form'.

ITEM 1 - ECG's
Please complete with the numbers of included ECGs:
- prior to the MI,
- at the time of MI (within hours/days of onset), and
- after the MI

Ensure that all ECG's are marked with pt ID code, ECG velocity, date and time.

ITEM 2 - Serology
Please record sequence and/or peak-values of measurements performed within 72 hours of the MI. For iso-enzyme peak-values and sequence of corresponding enzymes: CK and CK-MB, LDH-1 and LDH-2 are required.
For Troponin T and/or I the peak-value is sufficient, although the sequence is desired.

ITEM 3 - Additional ICP event
Please indicate whether the patient had an invasive cardiovascular procedure performed in relation to the MI event; if so please also complete an ICP form.

ITEM 4 - Summary
Please provide a brief narrative description of the event including information on duration and nature of the symptoms. Indicate whether the symptoms were typical (see section 4.1).

3.4 Event checking chart for cases of stroke (STR)

To be completed for patients who have experienced a stroke. For fatal cases, please also complete a CoDe form.

ITEM 1 – Type of stroke
Please complete whether the stroke has been identified due to:
Haemorrhage, infarction, sub-arachnoidal haemorrhage (SAH), or clinical stroke where the pathogenesis remains unknown.

ITEM 2 – Means of diagnosis
Record:
- Findings from the clinical examination
- Describe whether the neurological deficits are focal and/or global
- Include an estimate of the duration of the symptoms. Duration of less than 24 hours followed by complete remission of symptoms implies that the cerebral lesion was a 'Transient Ischemic Attack' – this diagnosis does not qualify as a stroke.

ITEM 3 – Examination of Cerebrospinal Fluid (CSF)
Indicate whether examination of cerebrospinal fluid has been conducted and provide a description of the findings (i.e. information on pleocytosis (white blood cells in CSF), xantochromi, CSF-protein and CSF-glucose).

ITEM 4 – Other etiology
Indicate whether the patient was diagnosed with other CNS pathology in association with the stroke, including evidence of space occupying lesions or evidence of CNS infection.

ITEM 5 – Underlying medical condition
Indicate whether the patient suffered from any medical condition known to be associated with increased risk of stroke (e.g. atrial flutter/fibrillation, hypertension)

ITEM 6 – Previous history of neurological disorder
Indicate whether the patient has a history of neurological disorder, HIV-related or not, and provide a brief description of the condition.

3.5 Event checking chart for Invasive cardiovascular procedures (ICP)

To be completed for patients who have undergone an invasive cardiovascular procedure.

ITEM 1 – Type of invasive cardiovascular procedure
Please complete if the patient has ever undergone a procedure of:
Coronary artery by-pass grafting, *Coronary* angioplasty/stenting (PTCA), or *Carotid* endarterectomy.

ITEM 2
Please indicate whether the procedure was associated with an MI and if the procedure was conducted as acute intervention during acute MI or complicated by an MI.
Please also complete an MI form in case of an MI.

ITEM 3
Please indicate whether the procedure was complicated by stroke.
If a stroke was present, please complete a stroke form as well.

ITEM 4
Please indicate whether copies of original source documents from the hospital record have been included in the report.

3.6 Event checking chart for cases of Diabetes Mellitus (DM)

To be completed for patients who have developed diabetes mellitus.

ITEM 1 – Blood sugar measurements
For the diagnosis of diabetes mellitus two elevated fasting blood sugar measurements are required (D:A:D definition: Fasting plasma-glucose >7 mmol/L

(126 mg/dL) measured on two independent occasions or one single value of NGSP haemoglobin A1c *(HbA1c) ≥ 6.5% (48mmol/l).* See Section 4.6 for additional details.

ITEM 2 – Other medical therapy
Please indicate if there is evidence that the DM is precipitated by other medical therapy (other than ART), e.g. therapy with corticosteroids, pentamidine or other.

ITEM 3 - Pancreatitis
Based on hospital records, please indicate if there is a current or previous medical history of pancreatitis (acute or chronic)?.

3.7 Event checking chart for fatal cases

In 2004 the CoDe (Coding Causes of Death in HIV) form replaced the event checking chart for fatal cases). The route of communication for the CoDe form is the same as for the other event checking charts. For details, we kindly refer to the CoDe Protocol.

Please ensure that all D:A:D events described on the CoDe form are also reported on a separate case report form.

3.8 Event checking chart for Cancers, both AIDS and Non-AIDS defining
To be completed for patients who have been diagnosed with any malignant disease both AIDS and Non-AIDS defining (excluding pre-cancers, relapses and basal or squamous cell skin cancer).

HEADING: The date of first diagnosis is the day, month and year the tumor was diagnosed for the first time by a medical practitioner, whether clinically or microscopically confirmed. If there is a relapse in the same primary location or dissemination from the same primary cancer, a new CRF does not need to be completed.

ITEM 1 Diagnosis
Please provide the specific type and the primary location of the cancer and if available the ICD-10 or ICD-9 code in the spaces provided in the CRF.

ITEM 2 Stage at diagnosis
Please tick the appropriate box (only one box) for the stage of the cancer at the time of diagnosis.

ITEM 3 Histology/cytology
Please indicate whether a pathology report is available after a biopsy.

If yes: please indicate whether copies of original source data have been included with the CRF and give a brief summary of the report in English in the space provided.

If no or unknown: please complete item 4.

ITEM 4 If the diagnosis is not confirmed by histology/cytology **please mark by which means the cancer was diagnosed and specify this in the space provided.**

ITEM 5 Prior history of chemo-and/or radiotherapy for a malignant disease
Please indicate in the appropriate boxes whether the patient has received chemo- and/or radiation therapy in the past or not. If yes, please indicate type and year of therapy .

3.9 Event checking chart for End-Stage Liver Disease (ESLD)

To be completed for patients who have experienced ESLD event. For fatal cases, please also complete a CoDe form

HEADING: The date of event is the day, month and year the first time the patient developed one of the clinical signs of liver failure listed in Section 4.8, sub-section A.1 **or** the day, month and year the patient had a liver transplantation performed.

ITEM 1 – Definition of endpoint
Please complete the CRF **the first time** the patient develops one of the clinical signs of liver failure listed in section 4.8 **or** if the patient has undergone a liver transplant. Please provide source documentation for the above.

ITEM 2 - Diagnosis
Please provide the specific diagnosis of the patient's liver disease in the space provided in the form. If available, please include the ICD-10 or ICD-9 code

ITEM 3 - Co-morbidities and risk factors
Please mark if the patient has been diagnosed with:

- **Chronic hepatitis B virus (HBV**)
  Chronic hepatitis B is inflammation of the liver that lasts at least 6 months
- **Chronic hepatitis C virus (HCV)**
  Chronic hepatitis C is inflammation of the liver that lasts at least 6 months
- **Current or past alcohol abuse**
  Alcohol abuse definitions[1]:
  For men: An intake of > 25 alcohol-containing units a week
  For women: An intake of > 20 alcohol-containing units a week

ITEM 4 - Documentation of presence of cirrhosis
Please indicate whether a liver biopsy or a fibroscan has been performed. If **yes** please indicate in the space provided the date of the most recent biopsy/fibroscan and the Metavir stage of fibrosis (F0-F4**:** F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, cirrhosis). Please indicate whether

[1] Definition of alcohol abuse for men and women are formulated on the basis of existing national guidelines, refer to http://www.icap.org/PolicyIssues/DrinkingGuidelines/GuidelinesTable/tabid/204/Default.aspx

copies of original source data have been included and give a brief summary of the report in English in the space provided.

3.10 Event checking chart for End-Stage Renal Disease (ESRD)

To be completed for patients who have been diagnosed with an ESRD event.

HEADING: The date of event is the day, month and year when the patient for the first time initiated permanent (lasting > 3 months) haemodialysis or peritoneal dialysis **or** the date the patient had a kidney transplantation performed.

ITEM 1 - Definition of endpoint
Please complete **the first time** the patient with has initiated permanent (expected to last at least 3 months) haemodialysis or peritoneal dialysis **or** if the patient has undergone kidney transplantation.
Please provide source documentation for the above.

ITEM 2 – Diagnosis and categories of renal disease
Please indicate the category that best applies to characterize the patient's renal disease. All of the diseases listed are diagnosed by a histology result, **except for** polycystic kidney disease.

If the specific diagnosis of the patient's kidney disease and the ICD-10 or ICD-9 code are available, please record these data in the space provided in the CRF.

ITEM 3 - Histology
Please indicate whether a kidney biopsy has been performed**.** If **yes** please indicate whether copies of original source data have been included and give a brief summary of the report in English in the space provided.

3.11 Route of communication – Event checking charts

Each cohort is in charge of the route of communication for event forms and event checking charts:

1. The event checking chart is completed by the local site and sent to the coordinating cohort centre. A copy of the completed chart should be kept on file at the site.

2. The coordinating cohort office reviews the information provided in the chart and if there is missing data in the chart or the site needs to attaché more source data, the coordinating cohort office should request this from the site.

3. The coordinating cohort office needs to forward the completed event checking chart to the CC in Copenhagen along with the relevant copies of original documents/source data from the medical record (see guide for all relevant and required source documentations in Appendix F). All information that can identify the patients like name, home address etc needs to be redacted from source data and marked with the study patient ID-code instead. Copies of the checking charts are kept at the coordinating cohort office.

4. The study coordinator at the CC reviews the event checking charts for completeness and may request additional information if necessary.

5. The cohort coordinating centre finally uses the event forms for source data verification of the event during monitoring visits to the site. It should be recorded in the monitor reports that source data verification has been done.

Any additional information that appears from the monitoring procedure is added to the event checking chart, and the chart is marked to indicate that monitoring was done. The completed chart is forwarded to the Study coordinating office (a copy is kept at the cohort coordinating centre).

4 Case definitions

In case of uncertainty of whether a patient fulfils the diagnostic criteria for one of the D:A:D endpoints, please contact the CC in Copenhagen for clarification.

The definition for an MI event in the D:A:D study has been prepared on the basis of the manual for the MONICA study (coronary event registration data component – website: http://www.ktl.fi/publications/monica/manual/), a study concerning coronary/stroke events and the characteristics hereof.

4.1 Definitive myocardial infarction (MI)

i) Definitive* electrocardiogram (ECG),
ii) Symptoms* together with probable* ECG and abnormal enzymes (or troponine)*,
iii) Typical symptoms*, abnormal enzymes* and ischaemic/non-codable/not available* ECG, or
iv)Fatal cases with naked-eye appearance of fresh MI and/or recent coronary occlusion found at necropsy.

4.2 Possible acute MI

Living patients with typical symptoms* whose ECG* and enzymes* do not place them as myocardial infarction and in whom there is no conclusive evidence for another diagnosis for the attack.

4.3 Possible coronary death

Fatal cases where there is no conclusive evidence for another cause of death, clinically or at autopsy:
a) With symptoms* (typical, atypical or inadequately described), or
b) History of previous chronic heart disease (definitive/possible MI, coronary insufficiency or angina pectoris in the absence of significant valvular disease or cardiomyopathy), or
c) Evidence of chronic coronary occlusion or stenosis or old myocardial scarring at necropsy.

4.4 Fatal case with insufficient data

Fatal case with no autopsy, no history of typical or atypical or inadequately described symptoms*, no previous history of chronic ischaemic heart disease, and no other diagnosis.

*See the next 2 pages for definitions

Table 1. Definitions of myocardial infarction (please refer to the text for details).

	ECG	**Cardiac enzymes**	**Symptoms**	**Comment**
Definite myocardial infarction				
i)	ECG typical	-	-	-
ii)	ECG probable	*and* Enzymes elevated	*and* Symptoms typical, atypical or not interpretable	-
iii)	ECG ischaemic, uncodable or not available	*and* Enzymes elevated	*and* Symptoms typical	-
iv)	-	-	-	Fatal cases with MI/ recent coronary occlusion found at autopsy
Possible myocardial infarction for living patients				
	-	-	Symptoms typical	-
Possible coronary death				
i)	-	-	Symptoms typical, atypical or inadequately described	*and* No evidence for other cause of death
ii)	-	-	-	Fatal cases with a history of previous chronic heart disease
iii)	-	-	-	Fatal cases with evidence of heart disease at autopsy
Fatal cases with insufficient data				
	-	-	-	No autopsy, no history of symptoms, no previous history of chronic ischaemic heart disease, and no other diagnosis.

ECG changes*
ECG typical, evolution of ECG from normal to highly pathological:
a) Development of Q waves: Progression of Q codes from no Q to a diagnostic Q is sufficient. Progression from no Q to an equivocal Q or from equivocal Q to a diagnostic Q must be accompanied by deterioration in the ST segment or the T wave. Any of these types of progression must be accompanied by a T wave progression on > 3 records, or
b) Evolution of an injury current which last more than one day: An ST segment elevation lasting more than one day and T wave progression on > 3 records.

ECG probable, evolution of ECG from normal to slightly pathological or from slightly pathological to highly pathological:
Evolution of depolarisation changes:
a) No major ST segment depression in one ECG record and another record with a major ST segment depression.
b) No ST segment elevation in one ECG record and another record with an ST segment elevation.
c) No major T wave inversion in one record and another record with a major T wave inversion.

ECG ischaemic, corresponding ECG abnormalities without evolution.

ECG uncodable: uncodable for technical reasons or because of the presence of suppression codes (suppress most other codes, please refer to the MONICA Manual for details: third degree A-V block, persistent Wolff-Parkinson White Pattern, artificial pacemaker, complete left bundle branch block, complete right bundle branch block, intraventricular block, ventricular fibrillation and asystole, idioventricular rhythm, and supraventricular tachycardia above 140/minute).

Cardiac enzymes elevated
The enzymes include creatine phosphokinase (CK) (and the MB isoenzyme of CK), lactic dehydrogenase, cardiac-specific troponin T and cardiac-specific troponin I. Documentation of increases in amino-transferases is also accepted.

Symptoms typical
Symptoms are typical when chest pain is present and characterised by:
• oppressive thoracic pain/ angina pectoris (any synonym for pain is acceptable such as "pressure", "discomfort", "ache")
• duration of more than 20 minutes, and
• no definite non-cardiac, or cardiac non-atherosclerotic cause.

Symptoms atypical
Symptoms should be coded as ‘atypical’ if the symptoms were not typical but there was one or more of the following conditions present:
• atypical pain
• acute left ventricular failure
• shock
• syncope
AND the absence of cardiac disease other than ischaemic heart disease
AND no definite non-cardiac or cardiac non-atherosclerotic cause.

(Note: acute left ventricular failure, shock or syncope, do not convert otherwise typical symptoms into atypical ones.)

Atypical pain would be pain recorded as of short duration or intermittent with each bout lasting for less than 20 minutes, or pain at an unusual site (upper abdomen, arms, jaw, neck).

Acute left ventricular failure means that diagnosis was made clinically or that the patient became severely breathless suddenly. Chronic heart failure or breathlessness getting worse over several days would not qualify.

**Diagnostic criteria: Q waves- any Q wave in precordial leads V2 , V3 or V4 is diagnostic (unless there is axis rotation in precordial leads). Equivocal Q wave is a wide and deep Qwave in leads III, aVR or V1 combined with no Q waves in all other leads. In all other leads a Q wave is abnormal if it is: 1) >0.04 sec in duration (i.e., one small square) or 2) at least one quarter the height of the R wave in the same QRS complex (except for lead aVL where it should be at least one half).*
ST deviation: in the normal ECG, ST depression should not exceed 1mm in leads I, II III, aVF and V and elevation should not exceed 2 mm in the same leads

4.5 Stroke

Rapidly developed clinical signs of focal or global disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death), with no apparent cause other than a cardiovascular origin. Secondary stroke caused by trauma should be excluded.

The differentiation between infarction and haemorrhage should be based on results of cerebral scanning or necropsy. In case of uncertainty (results not interpretable, or test not performed), please indicate so on the event form.

Global disturbance: this applies to patients with subarachnoid haemorrhage or deep coma but excluding coma of systemic vascular origin such as shock, Stokes-Adams syndrome or hypertensive encephalopathy.

Definitive focal signs:
• Unilateral or bilateral motor impairment (including dyscoordination)
• Unilateral or bilateral sensory impairment
• Åphasis/dysphasis (non-fluent speech)
• Hemianopia (half-sided impairment of visual fields)
• Diplopia
• Forced gaze (conjugate deviation)
• Dysphagia of acute onset
• Apraxia of acute onset
• Ataxia of acute onset
• Perception deficit of acute onset.

Not acceptable as sole evidence of focal dysfunction
• Dizziness, vertigo
• Localised headache
• Blurred vision of both eyes
• Dysarthria (slurred speech)
• Impaired cognitive function (including confusion)
• Impaired consciousness
• Seizures

(Although strokes can present themselves in this way, these signs are not specific and therefore, cannot be accepted as definite evidence for stroke.)

4.6 Diabetes mellitus

For a definite diagnosis, the definition used in the D:A:D Study is based on the ADA criteria (*Diabetes Care 20:1183–1197, 1997*):

- Fasting plasma glucose > 7.0 mmol/L (126 mg/dL)

The measurement of elevated plasma glucose should be repeated at least on two consecutive independent occasions (different dates), without interim normal plasma glucose levels.

In the absence of information on fasting plasma glucose levels, please describe whether the diagnosis was based on:

- Single value of NGSP haemoglobin A1c *(HbA1c) ≥ 6.5% (48mmol/l).*

- Symptoms of diabetes plus random blood glucose concentration ≥ 11.1 mmol/L (200 mg/dL), or

- Two-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test, or

- The diagnosis has been made elsewhere, and the patient has received dietary advice or has been started on anti-diabetic therapy (please include information on generic drug name).

4.7 Cancer, both AIDS and Non-AIDS defining

Case definition of Cancer

A. Diagnosis of cancer *(other than pre-cancers, relapse, basal and squamous cell skin cancers)* in a pathology report that established the diagnosis

B. Diagnosis of cancer *(other than pre-cancers, relapse, basal and squamous cell skin cancers)* in a hospital discharge summary or consultation note from the hospitalization or clinic visit during which the diagnosis was established

C. In the absence of **A** or **B**: Strong suspicion of cancer supported by (i) evidence from radiological or other imaging technique or (ii) biochemical assay

D. In the absence of **A**, **B** or **C**: Strong suspicion of cancer by visual inspection (e.g. skin metastasis, suspected malignant melanoma, tissue growth resembling cancer visualized during endoscopy/anoscopy) not explained by other known conditions.

Confirmed: A or B **Probable:** C **Possible**: D

4.8 End-stage Liver Disease

A.1 Clinical symptoms of end-stage liver failure in patients with chronic liver disease, based on the diagnosis documented in a clinical note of either

(i) bleeding from gastric or esophageal varices

(ii) hepatic encephalopathy stage III or IV

(iii) hepatorenal syndrome

A. 2 Liver transplantation documented in a clinical note

B. Pathology report or fibro-scan report documenting severe liver fibrosis or cirrhosis (Metavir F3 or F4 or fibroscan liver stiffness >= 8 kPa)

Confirmed: A1 and B; or A2 **Probable:** A1

4.9 End-stage Renal Disease

Case definition of End-stage Renal Disease

A. Hemodialysis or peritoneal dialysis expected to last at least three months documented in a clinical note

B. Kidney transplant, documented in a clinical note

Confirmed: A or B **Probable:** Not applicable

5 Reasons for discontinuation of antiretroviral treatment

A list of reasons for discontinuation of anti-retroviral treatment which includes the most frequent reasons experienced by physicians and patients. Please, if possible, indicate which of the statements listed below best explain the reason for discontinuation of antiretroviral treatment:

 Treatment failure (i.e. virological, immunological, and /or clinical failure)
 Abnormal fat redistribution
 Concern of cardiovascular disease
 Dyslipidaemia
 Cardiovascular disease
 Hypersensitivity reaction
 Toxicity, predominantly from abdomen/G-I tract
 Toxicity – GI tract
 Toxicity – Liver
 Toxicity – Pancreas
 Toxicity, predominantly from nervous system
 Toxicity, predominantly from kidneys
 Toxicity, predominantly from endocrine system
 Diabetes
 Haematological toxicity (incl. anemia)
 Hyperlactatemia / lactic acidosis
 Toxicity, not mentioned above
 Toxicity, any
 Pregnancy related
 Availability of more effective treatment (not specifically failure or side effect related)
 Structured Treatment Interruption (STI)
 Patient's wish/ decision
 Physician’s decision
 Other causes, not specified above
 Unknown

6 Causes of death

After the endorsement by all cohorts in D:A:D of the new project on Coding of Death in HIV patients (the CoDe project) was introduced in 2004, the collection on causes of death in D:A:D was changed. The causes of death is collected routinely during follow-up are listed below. In addition to this, and for all causes of death occurring after January 1st 2005, a CoDe form needs be completed (please refer to the CoDe Protocol).

7 Monitoring

7.1 Site monitoring

The quality assurance for the D:A:D study includes monitoring. Each participating cohort appoints a monitor, who is not in any way associated with the particular site in the cohort.
The monitoring must be performed at regular visits to all sites *at least once annually* to ensure that the data collection live up to the highest possible standards and expected reliability. This in accordance with the site questionnaire participating site investigators have signed before enrolment of patients, indicating their anticipated performance regarding data collection for the D:A:D study including reporting of endpoints.

Requirements for site monitoring:
- training of site personnel planned and coordinated by the respective cohort study coordinator (training materials available in Appendix D).

- availability of study documents - protocol and MOOP - must be ensured.

- depending on the regulatory system, the authorities in some countries may require a signed patient information and informed consent form for each patient participating in a cohort study. If that is the case, the monitor must verify that all enrolled patients have signed the informed consent form.

- at site visits a random review of at least 10% of all patients participating in the study must be performed by the monitor. The cohort is responsible for selection of patients for review; however, 100% of the records of patients who have died or experienced an event (i.e. cancer, MI, stroke, ESRD) must be reviewed. Targeted and systematic approaches searching for potentially missed events can be granted as an alternative to the 10% random monitoring.

- if the monitor becomes aware of a missed event (a D:A:D event not reported to the CC), the requirement for review increases to 25% of all the patients at the particular site. This should be clearly indicated in the monitoring report.

- at each visit the monitor must ensure that a complete and up-to-date patient identification log is available. This to uniquely identify the patient's record within the cohort.

- completion of a monitoring report on the outcome of monitor visits are mandatory for all visits. The report must contain specific information on the requirements mentioned above. A standardised monitoring report (Appendix C) has been made in order to attain homogeneous reporting but reports with similar contents are accepted, if preferred by the respective cohort.

- The reports must be submitted to the cohort and subsequently forwarded to the study coordinating office by fax within a month after the site visits have taken place.

- the monitor log must be signed at each monitor visit.

7.2 Source data verification

The monitor must have direct access to all subject files/records, laboratory reports and other relevant source data to ensure correct data entry in the case report forms and to verify the data collection.
Source data verification is undertaken at the regular monitoring visits during the D:A:D study as a quality assurance.
Source data verification is required for **items 1, 3, 4 and 5 on the enrolment *and* follow-up forms.**
Full cooperation by the investigator and other study personnel is expected. All records must be available for monitoring.

7.3 Cohort monitoring

In addition to site monitoring the cohort coordinating offices across the world will be monitored by the study coordinating office in Copenhagen at regular intervals. This quality assurance is performed in accordance with the requirements of participating cohorts outlined in the D:A:D Protocol.

8 Regulatory requirements

It is the responsibility of each participating site to ensure that all necessary documents and approvals - according to local/national regulations - are obtained before enrolling patients in the study. If applicable notify the applicable Medicines Agency and/or Data Surveillance Authorities.
Some countries may require patient informed consent before enrolment - for this purpose, please find a sample provided in Appendix E.

APPENDIX A – Lists of medication

APPENDIX B – Forms

APPENDIX C – Monitoring report and monitor log

APPENDIX D – Training material

APPENDIX E – Sample Patient Informed Consent

APPENDIX F– Guide checking charts

APPENDIX G – References

APPENDIX A – Lists of medication

Platelet Aggregation Inhibitors
Clopidogrel Bisulfate, Ticlopidine Hcl, Acetyl Salicylate(low), Dipyridamole, Trifusal

ACE inhibitors
Hypotensives, Ace Blocking Type: Benazepril Hcl, Captopril, Enalapril Maleate, Enalaprilat Dihydrate, Fosinopril Sodium, Lisinopril, Moexipril Hcl, Perindopril, Perindopril Erbumine, Quinapril Hcl, Ramipril, Trandolapril, Zofenopril
Hypotensives,angiotensin Receptor Antagonist: Candesartan Cilexetil, Eprosartan Mesylate, Irbesartan, Losartan Potassium, Telmisartan, Valsartan

Other antihypertensive agents
Alpha-Adrenergic Blocking Agents: Phentolamine Mesylate
Alpha/Beta-Adrenergic Blocking Agents: Carvedilol, Labetalol Hcl
Beta-Adrenergic Blocking Agents: Acebutolol Hcl, Atenolol, Betaxolol Hcl, Bisoprolol Fumarate, Carteolol Hcl, Celiprolol, Metoprolol, Fumarate, Metoprolol Succinate, Metoprolol Tartrate, Nadolol, Nebivolol**,** Penbutolol Sulfate, Pindolol, Propranolol Hcl, Sotalol, Timolol Maleate
Calcium Channel Blocking Agents: Amlodipine Besylate, Diltiazem Hcl, Diltiazem Malate, Felodipine, Isradipine, Mibefradil Di-Hcl , Nicardipine, Nifedipine, Nisoldipinel, Verapamil Hcl
Hypotensives,ganglionic Blockers: Mecamylamine Hcl, Hypotensives,miscellaneous: Pargyline Hcl
Hypotensives,sympatholytic: Alseroxylon, Bethanidine Sulfate, Clonidine Hcl, Debrisoquine Sulfate, Deserpidine, Guanabenz Acetate, Guanadrel Sulfate, Guanethidine Sulfate, Guanfacine Hcl, Lofexidine Hcl, Methoserpidine, Methyldopa, Moxonidine, Rauwolfia Serpentina, Rescinnamine, Reserpine, Rilmenidine Phosphate, Tolonidine Nitrate
Hypotensives,vasodilators: Doxazosin Mesylate, Hydralazine Hcl, Minoxidil, Prazosin Hcl, Terazosin Hcl
Loop Diuretics: Bumetanide, Ethacrynic Acid, Furosemide, Torsemide
Potassium Sparing Diuretics: Amiloride Hcl, Spironolactone, Triamterene
Thiazide and related Diuretics: Bendroflumethiazide, Benzthiazide, Chlorothiazide, Chlorthalidone, Cyclothiazide, Hydrochlorothiazide, Hydroflumethiazide, Indapamide, Methyclothiazide, Metolazone, Polythiazide, Quinethazone, Trichlormethiazide

Lipid lowering agents
Bile Salt Sequestrants: Cholestyramine, Colestipol Hcl, Cholestyramine/Aspartame, Cholestyramine/Sucrose
Lipotropics: Atorvastatin Calcium, Bezafibrate, Cerivastatin Sodium, Clofibrate, Clofibrate Magnesium, Dextrothyroxine Sodium, Ezetimibe, Fenofibrate, Fluvastatin Sodium, Gemfibrozil, Lovastatin, Pravastatin Sodium, Probucol, Simvastatin

Oral antidiabetic agents
Sulfonylureas: Acetohexamide, Carbutamide, Chlorpropamide, Glibenclamid, Glibornuride, Gliclazide, Glimepiride, Glipizide, Glliquidone, Glisoxepide, Glyburide, Glyburide Micronized, Tolazamide, Tolbutamide

Non-Sulfonylureas: Acarbose, Guar Gum, Metformin Ch-Phenoxyacetate, Metformin Hcl, Metformin Pamoate, Miglitol, Nateglinide, Phenformin Hcl, Pioglitazone, Repagllinide, Rosiglitazone

Insulin and derivatives hereof
Insulin Isophane, Insulin Lente, Insulin Lispro, Insulin Nph, Insulin Protamine Zn, Insulin R, Insulin Zinc

Other antidiabetic agents
exenatide and liraglutide (given in combination with oral drugs), sitagliptin.

Anabolic steroids and appetite stimulants
Anabolic steroids: Nandrolone, Oxandrolone, Oxymetholone, Stanozolol, Testosterone
Miscellaneous: megestrol acetate, dranabinol

APPENDIX B – Forms

• Enrolment

• Follow-up

• Event Forms:

-Myocardial Infarction

-Stroke

-Invasive Cardiovascular Procedures

-Diabetes Mellitus

-CoDe Form

-Cancer

-End-stage liver disease

-End-stage renal disease

DAD

Enrolment

Patient identification code_____Date of completion (dd/mm/yy) _____

Completed by _____

---

1. Have any of the following diseases/procedures ever been diagnosed/performed*:

a) Myocardial infarction	|__| Yes |__| No |__| Unknown	If yes,date of diagnosis (mm/yy): |_____|
b) Stroke	|__| Yes |__| No |__| Unknown	If yes,date of diagnosis (mm/yy): |_____|
c) Diabetes mellitus	|__| Yes |__| No |__| Unknown	If yes,date of diagnosis (mm/yy): |_____|
d) Coronary artery by-pass grafting	|__| Yes |__| No |__| Unknown	If yes,date of procedure (mm/yy): |_____|
e) Coronary angioplasty/stenting	|__| Yes |__| No |__| Unknown	If yes,date of procedure (mm/yy): |_____|
f) Carotic endarterectomy	|__| Yes |__| No |__| Unknown	If yes,date of procedure (mm/yy): |_____|
g) Cancer	|__| Yes |__| No |__| Unknown	If yes,date of procedure (mm/yy): |_____|
h) End-stage Liver disease	|__| Yes |__| No |__| Unknown	If yes,date of procedure (mm/yy): |_____|
i) End-stage renal disease	|__| Yes |__| No |__| Unknown	If yes,date of procedure (mm/yy): |_____|

*** All diseases need to meet the criteria for the DAD events listed in the DAD MOOP and the New DAD Endpoint Guidelines**

---

2. Have any first degree relatives (genetic mother, father, brother, sister) experienced myocardial infarction or stroke before the age of 50 years: |__| Yes |__| No |__| Unknown

---

3. Most recently measured:

	Not done	Fasting	Value	Unit	Date of measurement (mm/yy)
Serum total cholesterol	|__|	|__|	|_____|	|_____|	|_____|
Serum HDL cholesterol	|__|	|__|	|_____|	|_____|	|_____|
Serum triglycerides	|__|	|__|	|_____|	|_____|	|_____|

	Not done	Value	Date of measurement (mm/yy)
4. Systolic and diastolic blood pressure	|__|	|_____/_____|	|_____|

---

5. Ongoing treatment

	On treatment			On treatment	
a) Anti platelets	|__| Yes	|__| No	e) Oral antidiabetic agents	|__| Yes	|__| No
b) ACE inhibitors	|__| Yes	|__| No	f) Insulin or derivatives hereof	|__| Yes	|__| No
c) Antihypertensive agents,others	|__| Yes	|__| No	g) Anabolic steroids/appetite stimulants	|__| Yes	|__| No
d) Lipid lowering agents	|__| Yes	|__| No			

---

6. Is the patient currently a cigarette smoker |__| Yes |__| No |__| Unknown

If NO - has he/she ever smoked cigarettes |__| Yes |__| No |__| Unknown

---

7. Is the patient experiencing loss of fat from extremities, buttocks or face? |__| Yes |__| No

8. Is the patient experiencing accumulation of fat in abdomen, neck, breasts or other defined location? |__| Yes |__| No

D:A:D

Follow-up

Patient identification code _____Date of completion (dd/mm/yy) _____
Completed by _____

---

1. Have any of the following disease(s)/procedures been diagnosed/performed since D.A.D enrolment/ last follow-up*:

a) Myocardial infarction (definitive/possible)	|__| Yes |__| No	If yes,date of diagnosis (mm/yy):	|_____|
b) Stroke	|__| Yes |__| No	If yes,date of diagnosis (mm/yy):	|_____|
c) Diabetes mellitus	|__| Yes |__| No	If yes,date of diagnosis (mm/yy):	|_____|
d) Coronary artery by-pass grafting	|__| Yes |__| No	If yes,date of procedure (mm/yy):	|_____|
e) Coronary angioplasty/stenting	|__| Yes |__| No	If yes,date of procedure (mm/yy):	|_____|
f) Carotic endarterectomy	|__| Yes |__| No	If yes,date of procedure (mm/yy):	|_____|
g) Cancer	|__| Yes |__| No	If yes,date of procedure (mm/yy):	|_____|
h) End-stage liver disease	|__| Yes |__| No	If yes,date of procedure (mm/yy):	|_____|
i) End-stage renal disease	|__| Yes |__| No	If yes,date of procedure (mm/yy):	|_____|

*** All diseases need to meet the criteria for the DAD events listed in the DAD MOOP and the New DAD Endpoint Guidelines**

---

2. Have any first degree relatives (genetic mother, father, brother, sister) experienced myocardial infarction or stroke before the age of 50 years?

|__| Yes |__| No |__| Unknown

---

3. Most recently measured:

	Not done	Fasting	Value	Unit	Date of measurement (mm/yy)
Serum total cholesterol	|__|	|__|	|_____|	|_____|	|_____|
Serum HDL cholesterol	|__|	|__|	|_____|	|_____|	|_____|
Serum triglycerides	|__|	|__|	|_____|	|_____|	|_____|

	Not done	Value	Date of measurement (dd/mm/yy)
4. Systolic and diastolic blood pressure	|__|	|_____/_____|	|_____|

---

5. Ongoing treatment at time of this follow-up

	On treatment at current visit (Y=Yes, N=No, U=Unknown)	Start date (dd/mm/yy)	Stop date (dd/mm/yy)
a) Anti-platelets	|__|	|_____|	|_____|
b) ACE inhibitors	|__|	|_____|	|_____|
c) Antihypertensive agents, others	|__|	|_____|	|_____|
d) Lipid lowering agents	|__|	|_____|	|_____|
e) Oral antidiabetic agents	|__|	|_____|	|_____|
f) Insulin or derivatives hereof	|__|	|_____|	|_____|
g) Anabolic steroids/appetite stimulants	|__|	|_____|	|_____|

---

6. Is the patient currently a cigarette smoker |__| Yes |__| No |__| Unknown

---

7. Is the patient experiencing loss of fat from extremities, buttocks or face? |__| Yes |__| No

8. Is the patient experiencing accumulation of fat in abdomen, neck, breasts or other defined location? |__| Yes |__| No

D:A:D

Event Checking Chart

Cases of Myocardial infarction (MI)

Name of centre and cohort _____

Patient ID code:_____ Gender:_____

Year of birth (yyyy):_____ Date of event (dd/mm/yy):_____

---

1. Number of available ECG's, copies of which are included.

   Total (aim 3-6) __ Prior to MI (aim 1-2) ___ From time of MI (aim 1-2) __ After MI (aim 1-2) __

   Are all ECG's marked with: |__| pt ID-code, |__| date & time, |__| ecg-velocity?

2. Serological markers.

Register sequence of and/or peak-values of measurements performed within 72 hours of the event. (For iso-enzymes: peak-value of CK-MB and the corresponding value of CK, peak-value of LDH-1 and the corresponding value of LDH-2).

CK / unit	CK-MB / unit	Troponin T/ unit	Troponin I/ unit	LDH-1 / unit	LDH-2 / unit	Other serology marker– which? / unit	Time from MI / hours

3. Narrative description of the event/ Summary of symptoms.

Duration of symptoms (> 20 min.?): _____

Quality of symptoms, summary:

_____

_____

|__| Typical |__| Atypical |__| Description incomplete |__| No information available

4. Was an invasive cardiovascular procedure performed in relation to the MI: Yes |__| No |__|
   (*if yes, please complete an ICP event form*)

|__| All available information regarding this event has been collected,

For fatal cases, please also complete a CoDe form.

Signature:_____ the Study Coordinating Office, Date:_____(dd/mm/yyyy)

Monitored at site by: _____ _____ Date: _____
Print Name Signature dd/mm/yyyy

Please return this form to the DAD study coordinating office incl. ecg's & copies of other relevant documents from the medical record (made anonymous and labelled with the patients ID-code) by air-or email and keep a copy of the chart at the cohort coordinating office.

D:A:D

Event Checking Chart

Cases of Stroke (STR)

Name of centre and cohort _____

Patient ID code:_____Gender:_____

Year of birth (yyyy):_____Date of event dd/mm/yy):_____

---

1. Was the stroke identified as:
   Haemorrhage |__|Infarction |__| Subarachnoideal haemorrhage |__| Unknown |__|

2. Was the stroke diagnosed by (tick all applicable):
   |__| clinical presentation, findings (please provide source documentation): _____

_____

   Focal |__| Global |__|
   Duration of symptoms (> 24 hours?): Yes |__| No |__|

   |__| CT-scanning of cerebrum, findings:_____

   |__| MR-scanning of cerebrum, findings:_____

3. Has examination of cerebrospinal fluid been conducted? Yes |__| No |__|
   if yes, findings: _____

4. Is there an other aetiology for the patients symptoms?

   evidence of space-occupying lesions? Yes |__| No |__| Unknown |__|
   evidence of CNS-infection? Yes |__| No |__| Unknown |__|

5. Did the patient suffer from any medical condition, which could possibly have precipitated the stroke? Yes |__| No |__| Unknown |__|

if yes, please indicate which
condition:_____

6. Previous history of neurological disorder (HIV-related or other)? Yes |__| No |__| Unknown |__|
   If yes, please give a brief description: _____

_____

|__| All available information regarding this event has been collected

For fatal cases, please also complete a CoDe form.

Signature:_____the Study Coordinating Office, Date:_____(dd/mm/yyyy)

Monitored at site by: _____ _____ Date: _____
Print Name Signature dd/mm/yyyy

Please return this form to the DAD study coordinating office incl. copies of other relevant documents from the medical record (made anonymous and labelled with the patients ID-code) by air- or email and provide the cohort coordinating office with a copy of the chart.

D:A:D

Event Checking Chart

Cases of invasive cardiovascular procedures (ICP)

Name of centre and cohort _____

Patient ID code:_____ Gender:_____

Year of birth (yyyy):_____ Date of event (dd/mm/yy):_____

---

1. Which invasive cardiovascular procedure has been conducted?

   |__| Coronary artery by-pass grafting
   |__| Coronary angioplasty/stenting
   |__| Carotic endarterectomy

2. Was the procedure conducted in relation to a myocardial infarction?
   |__| no
   |__| yes - acute intervention during MI
   |__| yes - the procedure was complicated by an MI
   |__| yes - after MI

   (*if yes, complete checking chart for cases of MI*)

3. Was the procedure complicated by stroke?
   |__| no
   |__| yes (*if yes, complete checking chart for stroke*)

4. Have copies of original documents from the hospital record been collected?
   (Description of the procedure, coronary-arteriography, ecg's etc.)

   |__| yes, the following:_____

   _____

   |__| no, will be forwarded later

   |__| no, can not be obtained because:_____

   _____

|__| All available information regarding this event has been collected,

For fatal cases, please also complete a CoDe form.

Signature:_____ the Study Coordinating Office, Date:_____ (dd/mm/yyyy)

Monitored at site by: _____ _____ Date: _____
Print Name Signature dd/mm/yyyy

Please return this form to the DAD study coordinating office incl. ecg's & copies of other relevant documents from the medical record (made anonymous and labelled with the patients ID-code) by air- or email and keep a copy of the chart at the cohort coordinating office.

D:A:D

Event Checking Chart

Cases of Diabetes Mellitus (DM)

Name of centre and cohort _____

Patient ID code:_____ Gender:_____

Year of birth (yyyy):_____ Date of event (dd/mm/yy):_____

---

1. Has diabetes been diagnosed by repeated elevated fasting plasma glucose? yes |__| no |__|

   If yes, please indicate measurements on independent dates:

   date: / / fasting plasma glucose: unit:
   date: / / fasting plasma glucose: unit:

2. Has diabetes been diagnosed by NGSP HbA1c? yes |__| no |__|

   If yes, please indicate date_____ and measurement in %_____

3. Has the patient initiated anti-DM treatment? yes |__| no |__|

   If yes, please indicate date_____ and treatment_____

   If neither 1, 2, or 3, how was diabetes diagnosed?: _____

---

4. Did the patient receive any medical treatment, other than ART, that could have precipitated diabetes? yes |__| no |__|
   if yes, which therapy (please indicate drug by generic name)? : _____

   _____

5. Any current or previous medical history of pancreatitis? Yes |__| No |__| Unknown |__|

_____

|__| All available information regarding this event has been collected,

For fatal cases, please also complete a CoDe form.

Signature:_____the Study Coordinating Office, Date:_____(dd/mm/yyyy)

Monitored at site by: _____ _____ Date: _____
Print Name Signature dd/mm/yyyy

Please return this form to the DAD study coordinating office incl. copies of relevant documents from the medical record (made anonymous and labelled with the patients ID-code) by air-or email and keep a copy of the chart at the cohort coordinating office.

Cause of Death Form (CRF)

CoDe

*Study:_____

*Patient ID code: _____

*Date of death : ___–____– ___
(dd/mmm/yy eg 01-FEB-05)

If the patient experienced any D:A:D event(s), please report such event(s) on a designated D:A:D event form in addition to the completion of the CoDe form

Section 1♦ Background demographics

- * **A.** Year of birth (yyyy) __ __ __ __ **B**. Gender : ☐male ☐female
- **C.** Height (cm):__ __ __**D.** Weight (kg) : __ __ __ (most recent before death) **E.** Date :__ __ – __ __ __ – __ __ (dd-mmm-yy; weight measured)

Section 2♦ What data sources were available for the completion of this form? (please mark all that apply)

• **A.** Hospital files	☐Yes, complete	☐Yes, incomplete	☐No
• **B.** Outpatient clinic chart	☐Yes, complete	☐Yes, incomplete	☐No
• **C.** Autopsy report	☐Yes, complete	☐Yes, incomplete	☐No

- **If other, specify:**
- **D.** Registry ☐ • **G.** Patient's medical provider ☐
- **E.** Obituary ☐ • **H.** Nursing home ☐
- **F.** Patient's relatives or partner ☐ • **I.** Other:_____

Section 3♦ Risk factors:

A. Ongoing risk factors in the year prior to death:

1. Cigarette smoking	☐ Yes	☐ No	☐ Unknown
2. Excessive alcohol consumption	☐ Yes	☐ No	☐ Unknown
3. Active illicit injecting drug use	☐ Yes	☐ No	☐ Unknown
4. Active illicit non-injecting drug use	☐ Yes	☐ No	☐ Unknown
5. Opiate substitution (methadone)	☐ Yes	☐ No	☐ Unknown

Section 4♦ Co-morbidities:

A. Ongoing chronic conditions:

1. Hypertension	☐ Yes	☐ No	☐ Unknown
2. Diabetes mellitus	☐ Yes	☐ No	☐ Unknown
3. Dyslipidemia	☐ Yes	☐ No	☐ Unknown

B. Prior cardiovascular disease (*myocardial infarction, stroke or invasive cardiovascular procedure)*	☐ Yes	☐ No	☐ Unknown
C. History of depression	☐ Yes	☐ No	☐ Unknown
D. History of psychosis	☐ Yes	☐ No	☐ Unknown

E. Liver disease:

1. Chronic elevation of liver transaminases	☐ Yes	☐ No	☐ Unknown
2. Chronic HBV infection	☐ Yes	☐ No	☐ Unknown
3. Chronic HCV infection	☐ Yes	☐ No	☐ Unknown
4. HDV infection	☐ Yes	☐ No	☐ Unknown
5. History of previous liver decompensation	☐ Yes	☐ No	☐ Unknown
6. Clinical signs of liver failure in the 4 weeks before death	☐ Yes	☐ No	☐ Unknown
7. Liver histology available (ever)	☐ Yes	☐ No	☐ Unknown

***Please note that if any mandatory fields remain empty the CRF will not be registered**

***If Yes*, please indicate:**

the date of most recent biopsy _ _ - _ _ _ -_ _ the stage of fibrosis (0-4): |__|

(dd-mmm-yy eg 01-FEB-05)

Section 5♦ Cause of death

A. Was the death sudden? ☐ Yes ☐ No ☐ Unknown

B. Was the death unexpected? ☐ Yes ☐ No ☐ Unknown

C. Please complete the table below by recording all illnesses and conditions (acute and chronic) or injuries that the patient had at the time of death.

	Illness / Condition / Injury (text)	**Date of onset** dd/mmm/yy (eg 01-FEB-05)	**Certainty of diagnosis[a]**		
			Definite	Likely	Possible
1.		____ – _____– ____	☐	☐	☐
2.		____ – _____– ____	☐	☐	☐
3.		____ – _____– ____	☐	☐	☐
4.		____ – _____– ____	☐	☐	☐
5.		____ – _____– ____	☐	☐	☐
6.		____ – _____– ____	☐	☐	☐
7.		____ – _____– ____	☐	☐	☐
8.		____ – _____– ____	☐	☐	☐
9.		____ – _____– ____	☐	☐	☐

[a]**Certainty of Diagnosis: Definite=**95-100% certainty, **Likely=**80-95% certainty**, Possible=**50-80% certainty

***D. Brief narrative of the sequence of events leading to death (please include means of diagnosis of illnesses):**

_____

_____

_____

_____

_____

_____

***Please note that if any mandatory fields remain empty the CRF will not be registered**

E. In summary, the causal relation between the conditions leading to death was (complete this section with the corresponding number from table C above):

1. **Condition that directly caused death (immediate cause):**_____

2. Due to or as a consequence of :_____

3. Due to or as a consequence of:_____

4. **Condition that initiated the train of morbid events (the underlying condition):**_____

Section 6♦ Post-mortem / Autopsy:

A. Has autopsy been performed: ☐ Yes ☐ No ☐ Unknown

B. Did the autopsy reveal any evidence of intoxication?

☐ Yes, with the agent:_____ ☐ No ☐ Unknown

Please provide a brief summary of the findings from the autopsy report (please also include a copy of the full report):

Section 7 ♦ ART and laboratory values prior to death

A. Has the patient EVER received ART: ☐ Yes ☐ No ☐ Unknown

If YES, when was ART started (in months before death):

☐ ≤ 1 month before ☐ ≤ 3 months before ☐ ≤ 6 months before ☐ More than 6 months before

B. Did the patient receive ART at the time of death? ☐ Yes ☐ No ☐ Unknown

- ***If No***, Date of stopping __ __ – __ __ __ – __ __ **(dd/mmm/yy eg 01-FEB-05)**

C. Laboratory values (please complete all fields where data is available)

Laboratory values	Time	Value	Unit	Date dd/mmm/yy (eg 01-FEB-05)
CD4+ cell count	1. Most recent prior to last stopping ART		Cells/mm^3	__ __ – __ __ __ – __ __
	2. Most recent prior to death		Cells/mm^3	__ __ – __ __ __ – __ __
HIV RNA	1. Most recent at time of stopping ART		Copies/mL	__ __ – __ __ __ – __ __
	2. Most recent prior to death		Copies/mL	__ __ – __ __ __ – __ __
Haemoglobin	Most recent prior to death		/	__ __ – __ __ __ – __ __

***Please note that if any mandatory fields remain empty the CRF will not be registered**

Cause of Death Form (CRF)

CoDe

*Study:_____

*Patient ID code: _____

Section 8 ♦ Adverse effects to any type of medical treatment

A. Was the death considered to be related to a medical treatment? ☐ Yes ☐ No ☐ Possibly

B. The suspected relation was to: ☐ Antiretroviral treatment ☐ Other medical treatment

Please provide a brief narrative of the suspected association including the name of the medication and the date of starting:

_____

_____

_____

_____

Please refer to the 'CoDe instructions' for definitions and guidelines for the completion of this form

---

Completed by: Name (in print) _____

Position : ☐ Physician ☐ Nurse ☐ Other, describe _____

Directly involved in the medical care of the patient around the time of death? ☐Yes ☐ No

Date (dd/mmm/yy)**:**__ __ – __ __ __ – __ __ **Signature:** _____

***Please note that if any mandatory fields remain empty the CRF will not be registered**

D:A:D

Event Checking Chart

Cases of Cancer, both AIDS and Non-AIDS Defining Cancers

Name of centre and cohort _____
Patient ID code:_____ Gender: [ ] Male [ ] Female
Year of birth (yyyy):_____ Date of first diagnosis (dd/mm/yy):_____

---

1. Diagnosis

Please complete this form if the patient has been diagnosed with a malignant disease *(excluding pre-cancers, relapses, basal and squamous cell skin cancers)*

For the patients' cancer disease, please provide specific type: _____
(e.g. adenocarcinoma, osteosarcoma, leukemia)

Primary location *(if known)*: _____ *(e.g. lung)*; unknown [ ]

If available, please include the: ICD-10 _____, or ICD-9 code _____

2. Stage (spread) at diagnosis *(Tick one only):*

[ ] Localized (growth within the organ of origin)
[ ] Disseminated (spread to tissue outside the organ of origin, incl to regional lymph nodes)
[ ] Unknown

3. Histology/cytology

Is a pathology report (or summary hereof) available?
[ ] Yes, full report [ ] Summary of report [ ] No [ ] Unknown
If 'no' or 'unknown', please complete Question 4

If yes, please include a copy of the full report *(And provide a brief summary in English):*

_____
_____
_____

4. If the diagnosis is not confirmed by histology/cytology, is the diagnosis based on

(Tick all that apply, 1 at a minimum, and please provide source documentation):

I. [ ] Radiology or other imaging technique (cancer suggestive findings)
II. [ ] Biochemical assay (elevated markers of cancerous growth (e.g. prostate specific antigen, alpha-fetoprotein, cancer cell markers)
III. [ ] Strong suspicion of cancer by clinical inspection (skin metastasis, suspected malignant melanoma, suspected cancerous growth visualized during endoscopy/anoscopy)
IV. [ ] Other

Of those marked above, please specify:_____

5. Has the patient previously received chemo- and/or radiation therapy for a malignant disease? [ ], Yes [ ], No [ ], Unknown
If yes, please tick off the appropriate box: chemotherapy [ ], radiation [ ], year of treatment: _____
For fatal cases, please also complete a CoDe form.

Signature:_____the Study Coordinating Office, Date:_____(dd/mm/yyyy)

Monitored at site by: _____ _____ Date: _____
Print Name Signature dd/mm/yyyy

Please return this form to the DAD study coordinating office incl. copies of other relevant documents from the medical record (made anonymous and labeled with the patients ID-code) by air- or email and provide the cohort coordinating office with a copy of the chart.

D:A:D

Event Checking Chart

Cases of End-Stage Liver Disease- Severe Clinical Manifestations (ESLD)

Name of centre and cohort _____
Patient ID code:_____ Gender: [ ] Male [ ] Female
Year of birth (yyyy):_____ Date of Event in Question 1 (dd/mm/yy):_____

---

1. Definition of endpoint

Please complete this form only if the patient has developed one of the following clinical signs of ***liver failure*** for the first time (*and please provide source documentation*):

[ ] bleeding from gastric or esophageal varices (endoscopy verified)
[ ] hepatic encephalopathy stage III or IV (pre-coma or coma)
[ ] hepatorenal syndrome (acute renal failure in patient with existing severe chronic liver disease)

or ,

[ ] the patient has undergone liver transplantation

2. Diagnosis

Please provide the specific diagnosis of the patients liver disease: _____
If available, please include the ICD-10 _____or ICD-9 code _____

3. Co-morbidities and risk factors

Is the patient known with:
Chronic HCV? [ ] Yes [ ] No [ ] Unknown
Chronic HBV? [ ] Yes [ ] No [ ] Unknown
Current or past alcohol abuse? [ ] Yes [ ] No [ ] Unknown

4. Documentation of presence of cirrhosis

A. Has liver biopsy been performed? [ ] Yes [ ] No [ ] Unknown
B. Has fibroscan of the liver been performed? [ ] Yes [ ] No [ ] Unknown

If ***Yes*** to A or B, please indicate:
the date of most recent biopsy/ fibroscan (dd/mm/yy) __ __ – __ __ – __ __ and Metavir stage of fibrosis (F0-F4): |__|

Please include a copy of the full report *(and please provide a brief summary in English):*

_____
_____
_____

For fatal cases, please also complete a CoDe form.

Signature:_____the Study Coordinating Office, Date:_____
dd/mm/yyyy

Monitored at site by: _____ _____Date: _____
Print Name Signature dd/mm/yyyy

Please return this form to the DAD study coordinating office incl. copies of other relevant documents from the medical record (made anonymous and labelled with the patients ID-code) by air- or email and provide the cohort coordinating office with a copy of the chart.

D:A:D

Event Checking Chart

Cases of End-Stage Renal Disease (ESRD)

Name of centre and cohort _____

Patient ID code:_____ Gender: [ ] Male [ ] Female

Year of birth (yyyy):_____ Date of Event (dd/mm/yy):_____

---

1. Definition of endpoint

For the patient with *chronic renal disease*, please complete this form (and please provide source documentation) *the first time* the patient has initiated permanent (expected to last at least 3 months) dialysis:

[ ] hemodialysis

[ ] peritoneal dialysis,

or

[ ] the patient has undergone kidney transplantation

2. Diagnosis and categories of renal disease

Please indicate which category applies best for the characterization of the patients' renal disease *(tick one or more as appropriate)*:

Chronic renal failure, with underlying etiology

[ ] HIV associated nephropathy
[ ] glomerulonephritis
[ ] interstitiel nephritis
[ ] polycystic kidney disease
[ ] hereditary / congenital
[ ] vascular
[ ] diabetic nephropathy
[ ] systemic disease
[ ] other
[ ] unknown

If available, please provide the specific diagnosis of the patients' kidney disease:_____ and please include the ICD-10 _____or ICD-9 code _____

3. Histology

Has kidney biopsy been performed? [ ] Yes [ ] No [ ] Unknown

If yes, please include a copy of the full report *(and please provide a brief summary in English):*

_____

_____

_____

For fatal cases, please also complete a CoDe form.

Signature:_____the Study Coordinating Office, Date:_____(dd/mm/yyyy)

Monitored at site by: _____ _____Date: _____

Print Name Signature dd/mm/yyyy

Please return this form to the DAD study coordinating office incl. copies of other relevant documents from the medical record (made anonymous and labelled with the patients ID-code) by air- or email and provide the cohort coordinating office with a copy of the chart.

APPENDIX C – Monitoring report and monitor log

D:A:D

Monitoring visit Report

Name of cohort

Name of site **Site no.**

Principle investigator

Date of visit

Tick box and please write comment no. referring to the comments page

	Yes	No	Comment No.
Protocol / MOOP available	☐	☐	
Patient information/informed consent (if needed)	☐	☐	
Monitor log	☐	☐	
Training of site personnel	☐	☐	
Source data available	☐	☐	
Accurate patient identification list/patient log	☐	☐	
10% source data verification*	☐	☐	
25% source data verification**	☐	☐	

(Requirements for Source data verification are specified in the MOOP in section 7.2) *Please find enclosed a list for documentation of reviewed records
**If any missed events, 25% source data verification is required

This report consists of _____ pages.

Completed by (signature of monitor) **Date**

Reviewed by (signature of cohort coordinator) **Date**

D:A:D

Monitoring visit report

Source data verification – a random sample of records

Patient ID code	Missed events	Comment No.	Findings	Comment No.
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	
	No Yes		No Yes	

Please copy if additional pages are needed

D:A:D

Monitoring visit report Page ___

Comments:

(please indicate no.)

Please copy if additional pages are needed

Monitor log

Cohort : _____ Country :_____

Investigator: _____ Site code:_____

Hospital: _____

Date of visit (dd/mm/yy)	Signature of monitor	Purpose of visit	Signature of site representative

May 1st 2000
Version 1.1

APPENDIX D – Training material

Please see www/cphiv.dk/DAD for the Training Material

APPENDIX E – Sample Patient Informed Consent

The full nature of the D:A:D study has been explained to me.
I have read the patient information sheet and have been given the opportunity to ask questions and these have been answered to my satisfaction.
It has been explained to me that in case of my death, my next of kin may be approached for a medical release form.*
It has been explained that I can withdraw my consent at any time for any reason.
It has also been explained to me that authorised personnel may review my record but that identifiable information under no circumstances will be made publicly available.

I consent to enter the above mentioned study

Name_____
Signature_____Date_____

Investigator
Name of doctor_____
Signature_____Date_____

*Optional; can be included if local standards require.

APPENDIX F- Guide checking charts

Checking chart	Requested source documents	Report first or any event
Myocardial infarction	Up to 4 ECG, hospital report	any
Invasive cardiovascular procedure Coronary angioplasty, coronary bypass surgery, carotic endarterectomy	Report of intervention	any
Stroke Ischemic or hemorrhagic	Hospital report Especailly clarifying duration >< 24 hours and clinical symptoms	any
Diabetes	none	First diagnosis
End stage renal disease Haemodialysis, peritoneal dialysis, renal transplantation	Hospital report Especially clarifying dialysis duration >3 months/ transplantation Histology report or other information on how diagnosis was established	First of these events
Chronic liver disease Hepatic encephalopathy stage III-IV Bleeding from oesophageal varices Hepato-renal syndrome Liver transplantation	Hospital report on clinical symptoms/transplant Report of liver biopsy or report of fibroscan	First of these events
Cancer	Histology report Or if not availble imaging findings, discharge letter	First diagnosis only for each cancer type, not for a relapse

APPENDIX G- References

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